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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/211,715	12/14/1998	FAHAD AL-OBEIDI	P-SE-3243	9543

23601 7590 05/09/2002

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EXAMINER
LIU, SAMUEL W

ART UNIT	PAPER NUMBER
1653	21

DATE MAILED: 05/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/211,715	AL-OBEIDI ET AL
	Examiner	Art Unit
	Samuel W Liu	1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-11 and 20-26* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-11 and 20-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4)☐ Interview Summary (PTO-413) Paper No(s) _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other

DETAILED ACTION

The response filed on 3 January 2002 (paper 30) has been received and entered. Amendments of Claims 2, 3, 11 and 21, cancellation of Claims 1 and 12-19, and the extension for three months have been entered. Also, restatement of domestic priority with regard to the instant application in the applicants' amendment is acknowledged.

Claims 2-11 and 20-26 are pending to which the followings are or remain applicable. Please note that ground of objection and/or rejection not explicitly restated and/or set forth below are withdrawn.

Objection to Specification

The disclosure is objected to because of the following informalities:

(1) The abstract of the disclosure is objected to because the abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. Correction is required. See MPEP § 608.01(b). The language should be clear and concise.

(2) In abstract, line 10 "organic structure" should be changed to "chemical structure".

Correction is required and clarification to the numbering scheme of "-$CR_{99}R_{100}$" is also required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-11 and 20-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for Y-I-R containing compounds or closely related analogues, does not reasonably provide enablement for a general formula claimed and its utilization. The specification does not enable a skilled in the to which it pertains, or with which it is most nearly concerned, to make and use the commensurate in scope with these claims.

In this regards, the application disclosure and claims have been compared per the factors indicated in the decision *in re* Wands 8 USPQ2d 1400, 1400 (Fed. Cir. 1998) as to undue experimentation. The factors include: 1) the nature of the invention; 2) the breath of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art;

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

1) The nature of the invention

Claims 24-25 are directed to a method of using synthesized peptides based on specificity of inhibiting the enzymatic activity of factor Xa as determined by the common motif Y-I-R (tyrosine-Isoleucine-Arginine). Y-I-R represents an enzymatic *substrate analogue* of factor Xa that has relatively high affinity for the enzyme binding. Thus, any structural variants deviate from the common motif will not have selectivity on inhibiting factor Xa protease. Moreover, potency of the synthesized peptides of inhibiting Xa protease is unpredictable as to unpredictable selectivity of the produced peptides acting as specific Xa-inhibitors

In the claims 2-11 and 20-23, as presented do not have a common core structure containing a Y-I-R sequence. Claim 2 and its dependent claims set forth a very diverse formula from which Claim 24-25 depend. Because the method set forth by Claims 24 and 25 is dependent upon the inhibitor's specificity toward factor Xa protease.

The specification of the instant application sets forth that all the synthesized peptides contain at least one Y-I-R motif or functional equivalents thereof, and are capable of specially inhibiting factor Xa activity [see abstract, page 5, line 15-17, page 8 line 20-23 and "Summary of the Invention" (page 5-6)]. The Y-I-R motif is therefore necessary common core sequence in the specification. Furthermore, example XXXVI sets forth specific inhibition of factor Xa activity by compounds containing Y-I-R and closely related structural derivatives that have the inhibitory activity (see Table 3-5 also). The claims, however, recite broad formula (Claim 2) encompassing numerous substitution combinations, which are diverse from the common core structure disclosed in the specification.

Under these circumstance, some claims under consideration do not recite the core motif expressly, and the specification teaches 1) the invention is directed to Y-I-R peptides in which the Y-I-R motif determines both specificity and efficacy of the peptides; and 2) the inheritance of the specificity of inhibiting factor Xa within the core motif, thus, the scope of enablement is not commensurate with the scope of claims, i.e scope of the claims.

2) The breadth of the claims

The instant claims do not recite the critical core structure critical to Xa inhibition. Instead, claims are broadly drawn to a multitude of compounds derived from a general formula A1-A2-$(A3)_m$-B, which encompass a multitude of unrelated chemical moieties or groups, while the

specification discloses the core containing structures and their uses. Thus, scope of claims is broader than that of the specification, which does not render the invention enabling.

3) The unpredictability

There is an unpredictable degree of diversity from this core structure and it is highly variant, the invention is unpredictable in the absence of factual indicia to the contrary.

4) The amount of direction or guidance presented

The instant specification presents only limited guidance for Y-I-R core containing peptides and their functional assays. Potential candidate exerting inhibitory activity against Xa protease all possess the core or the core-like motif (see example XXXV, XXXVI and Table 3). It is apparent that structures deviating from inherent core motif Y-I-R would require undue guidance in order for using synthesized peptides. Those structures would represent various structural variants that are unpredictable, and therefore would give rise to unpredictable activity in view of structure-function relationship. Hofmann K. J. et al (*Biochem. J.* (1992) Vol. 287, 943-949) demonstrate that substitution of a critical amino acid residue (Arg (34)) will abolish the activity of studied protein.

5) The quantity of experimentation necessary:

In the absence of working examples with regard to the above mentioned numerous variant sequences, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trial and error to practice the claimed invention. Because of the reasons forgoing, the quantity of experimentation would be large and unpredictable because the skilled artisan would have been required to carry out a large

body of tests for screening and making any variant(s) that is (are) of desirable inhibitory activities against Xa protease without a prior expectation of success.

(6) The relative skill of those in the art:

The general knowledge and level of skill in the art a Ph.D. with several years of experience do not supplement the omitted description with respect to a massive number of variant sequences of polypeptide. In view of the preceding factors (1-5), the level of skill in this art is high and requires at least an organic chemist or a biochemist with several years of experience in protein manufacturing as well as knowledge in organic synthesis art, peptide chemistry, enzymology; yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable.

The variant peptides fall into unanticipated or/and abolished activities (see Hofmann K. J. et al, *Biochem. J.* (1992) Vol. 287, 943-949). Hofmann et al. show that substitution of a critical Arg (34) with other amino acid residue (except Lys residue) results in a dramatic decrease of inhibitory activity (i.e. increase IC_{50} (nM) value) of a Xa-inhibiting protein, antistasin (119 amino acid residues). In order to maintain a reasonable inhibitory spectrum, the skilled artisan are required unduly level of skill in order to identify clones that generate the desirable peptides of specific Xa-inhibiting activities.

The present claims recite a very broad formula (Claim 2) encompassing a large body of substitution combinations, which are very much diverse from the common core structure disclosed in the specification. This would not allow the artisan to practice the invention because vital common core motif is not inherent in claims. Thus, undue experimentation is needed.

In consideration of each of factors stated above, there is undue experimentation because of variability in prediction of outcome that is not addressed by the instant application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

Applicants' comments (page 10-16) in the response filed 3 January 2002 has been fully considered but they are not persuasive.

Applicants assert that claims teaches all of the structural elements that define the present invention and that all the substitution are defines as to their points of attachment, and to the chemical groups that are included. Applicants also assert that the "common core" is defined in terms of a compound with a peptide backbone that is variously substituted and the substituted compounds asserted exhibit the specific inhibitory activity of Factor Xa.

The instant application teaches all of structural element and substitutions, the application fails to disclose the core structure that is critical for determining specificity and potency of the synthesized compounds that act as Xa-protease inhibitors. Applicants set forth general formula A1-A2-$(A3)_m$ –B, which encompass a multitude of unrelated chemical moieties or groups (se substitutions of each R_1-R_9 including R'_1 and R''_1). Therefore, the formula does not represent a core structure, (note that in view of the comment at the bottom of page 11, any change to a moiety would be equivalent to a change in the core structure; thus, substitutions as argued in paragraph bridging pages 11-12 is unpersuasive of applicant's position), in which selectivity and potency of the inhibitors are inherent. Further, the formula is not defined in term of peptide backbone. In the instance, as claimed, X is N, if as elected R_2 is any substituted group in claim1, the constructed moiety of compound does not read on peptide backbone at all. Because of

unpredictability inherent in the structures, the resultant variants would not necessarily exhibit utility, i.e. selectively inhibiting Xa protease with an appreciable efficacy (potency).

Applicants' response asserts Examples XXXV-XXXIX as teaching an assay for, and, activities of the synthesized compounds in the instant application. It is noted that in fact, Example XXXV and XXXVI (Table 3) show the Y-I-R core motif derived compounds and activities. It also noted that the *Ki* "window" being used to activity screening is 100 μM (i.e. 10,0000 nM) by the instant application. Example XXXVI exhibits the potency and selectivity of Y-I-R derived compounds: one of them, Ac-(iBu) Y-I-R-I.-P shows *Ki* = 40 nM (Page 77, line 19). Hofmann et al. have shown that a mutant inhibitor (antistasin, a Xa protease inhibitor) decreases potency 6000-fold with comparison to the wild type (*Ki* = 1660 nM versus *Ki* = 0.27 nM, respectively). Thus, the *Ki* window set forth by the instant application does not appear to reflect intrinsic potency as well as selectivity of the synthesized compounds. Thus, it would appear that this particular, and, other results would have been predictable from the present application disclosure without first having to do experiment to see whether or not the *Ki* was of the appropriate value.

In addition, page 13* of the response refers to various examples, but it is not apparent from the explanation how this is reflective of the full scope of the recited formula, especially where each variable moiety is independently selected from any other moiety. The number of combinations of selection of moieties is at least a combinational number of A_1^3 by A_2^3 by A_3^3, and then further modified by combination with each R_1 to R_9 to start off with. Thus, insofar as applicant's response points to various tables in the specification, this falls far short of the scope of the current claims.

As stated above in the section of the rejection under USC 112, first paragraph, scope of claims of the instant application is broader than that of the specification, which does not render the invention enabling.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-3, 9, 11, 22, 24 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 contains an inappropriate Markush-type wording in the claim because the term "and" should not be followed by more one members, wherein are the member "(4-cyanophenyl)methyl" followed by the other "(4-hydroxyphenyl)methyl" (see page 4, line 5). This renders the claim indefinite.

Claim 2 is indefinite as to the term "Leu-OH" (in page 5, line 4) that is undefined in the specification. Is the hydroxyl group attached to carboxyl terminus of leucine or to one of methyl moieties? The same are Claim 3, 9 and 11.

Claim 22 is also indefinite because the claim sets forth a compound in which "-Pal (Me)" is unclear as to what "Me" means since the specification has not defined "Me" alone but "PalMe" that refers to as β-(3-N-methylpyridinium)-alanine.

Claim 24 and 26 are dependent from a cancelled claims, Claim 1and Claim 12, respectively, which render the claims indefinite.

Applicants comments (page 17-18) in the response filed 3 January 2002 has been considered. Applicants have amended Claim 21 that sets forth a synthetic peptide; but it is virtually identical to the peptide set forth in the preceding Claim 20; thus, Claim 21 should be deleted.

In addition, the response filed 3 January 2002 in the section of "Rejection under 23 U.S.C. 112, first paragraph" states that applicants have amended Claim 2 so that the claim is in proper form; however, the statement is unpersuasive because Claim 2 contains inappropriate Markush claim terminology. For the details, please see the following stated ground of rejection under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The Claims 2-3 are rejected under 35 U.S.C. 102 (e) as anticipated by or, in the alternative as obvious under 35 U.S.C. 103(a) 35 U.S.C. 103(a) over Brunck T. K. et al (US Patent 5739112). Although the invention is not identically disclosed or described as set forth in 35 U.S.C. 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a designer having ordinary skill in the art to which said subject matter pertains, the invention is not patentable.

It is noted that US patent 5739112 is continuation of Application (SN: 168964) whose filling date is 15 December 1993; thus, the effective filing date for 5739112 is15 December 1993.

Although Brunck et al do not set forth the general formula A_1–A_2–(A_m)-B in the instant application, the 5739112 patent dose disclose compounds that read on the said formula (see Patent, Claims 1-10 and Table 1-2) and the disclosed compounds are potent and specific as inhibitors of mammalian factor Xa (see Patent, Abstract and columns 1-5 and 8). Thus, the subject matter claimed in the instant application would have been anticipated if not obvious o one of ordinary skill in the art.

, The comments in the response filed 3 January 2002 at Page 19-22 have been considered. But they are unpersuasive.

Applicants asserted that in review of the prosecution record based on the ground of rejection under 35 USC 102 and 103, there was no assertion that Brunk's priority date to December 15, 1993.

The argument is not persuasive. US patent 5739112 is continuation of Application (SN: 168964) whose filling date is 15 December 1993; thus, the effective filing date for 5739112 is 15 December 1993.

Applicants also assert that the full scope of claim 1 to 11 of the present application are taught in the parent application, and that the compounds taught in Example XXXIV were taught generically in the parent application, and are encompassed within the breath of the issue parent claims.

The argument is not persuasive. US patent 5849510 (previously co-pending with the instant application) discloses the Y-I-R core motif that is important for the selectivity and potency of the synthesized compounds and the core structure closely derived analogues. The instant application sets forth a "genus", i.e. the general formula (see the above) which appears to embrace the structures (species) claimed in Patent 5849510. However, genus is not and does not necessarily disclose "species". The instant application fails to adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. Where, as here, the claimed *genus*, a general formula, represents a diverse and relatively poorly understood members of substitution chemical groups, even chemical bodings (backbones), as argued by applicants, between the groups are poorly defined, said genus would not inherently disclose all species. Note that applicant's response admits of new matter. New matter covered by the instant claims is not entitled to an earlier date since it is not earlier disclosed in the parent application. See the statement at pages 20-21 of the instant response.

In view of the foregoing, it is not apparent from the explanation at page 21, what claims are fully disclosed as a completed invention at an earlier date than the current application filing date.

Claim Rejection –Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed.

Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

Claims 2-6, 8-10, 23, 25 and 26 are rejected under the judicially created doctrine of the obviousness-type double patenting of the claim in United States Patent 5849510. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 1of Patent 5849510 discloses the identical formula as that of Claim 2 of the instant application. All compounds of Claim 1 (Patent 5849510) read on those of Claim 2 (the instant application). See also Claim 17 of Patent 5849510 versus the instant Application Claims 3-6; Claims 42 and 43 of Patent 5849510 versus Claims 25 and 26 of the instant application. Also, the subject of Claims 8-10 and 20 of the instant application are recited in Claim 22 of Patent 5849510. Therefore, the claims of the present application are not patentably distinct from the claims of US Patent 5849510.

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

It is noted that page 22 of the response filed 3 January 2002 requests abeyance of the obvious-type double patenting rejection until allowable subject matter is indicated. Note that no

allowable subject matter can be indicated with a standing ground of rejection. Thus, it is suggested that applicant file the appropriate terminal disclaimer.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483.

The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Christopher S. F. Low

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May 7, 2002